Pilot Studies of Thalidomide in Acute Myelogenous Leukemia, Myelodysplastic Syndromes, and Myeloproliferative Disorders

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The management of acute myeloid leukemia (AML), high-risk myelodysplastic syndromes (MDS), and myeloproliferative disorders remains challenging because of the inability of even the most effective treatment strategies to produce durable complete remissions. Bone marrow transplant (BMT) is one such modality with potentially curative benefit; however, its applicability generally is limited to patients of younger age with suitable donors. Therefore, novel agents and alternative therapeutic strategies need to be studied. The role of angiogenesis in hematologic malignancies has been elucidated by several investigators; hence, inhibitors of angiogenesis are being studied in these disorders. Thalidomide appears to have both antiangiogenic and immunosuppressive properties and has shown promising results in the treatment of refractory or relapsed multiple myeloma and plasma cell leukemia. Consequently, pilot studies of thalidomide for the treatment of other hematologic disorders, including refractory/relapsed AML, high-risk MDS, myeloproliferative disorders, and myelofibrosis are underway at M.D. Anderson Cancer Center. Preliminary results indicate that thalidomide has activity and is well tolerated in the treatment of these hematologic disorders, and thus warrants further evaluation.

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DESPITE RECENT PROGRESS in the treatment of acute leukemias, only 25% to 30% of adult patients are cured.[1-3] Although prognosis varies among acute myeloid leukemia (AML) subtypes, most patients relapse following an initial complete response (CR) and ultimately die of resistant disease. Patients with AML who experience a particularly short first CR and those who fail to achieve CR after two induction attempts are unlikely to respond to any currently available chemotherapeutic agents. Similarly, patients with high-risk myelodysplastic syndromes (MDS) likely to progress to AML (refractory anemia with excess blasts [RAEB] or refractory anemia with excess blasts in transformation [RAEB-T]) have an estimated survival of less than 1 year.[4] The standard of care for this population remains supportive therapy since intensive chemotherapy regimens, such as those used in AML, have been reported to produce high rates of treatment-related mortality with rare durable remissions.[5] Less intensive chemotherapy combination regimens can result in remissions with reduced mortality; however, achieving true disease eradication remains problematic.[4]

Chronic myelogenous leukemia (CML) is characterized by the presence of Philadelphia chromosome (Ph) in up to 95% of cases with a biphasic or triphasic disease course.[6] Most patients present with chronic-phase CML and can be effectively managed with interferon alfa–based therapy or allogeneic bone marrow transplantation (BMT).[6,7] Patients who fail to respond to interferon and are ineligible for BMT have limited treatment options available, although a few agents such as homoharringtonine and tyrosine kinase inhibitors show promise. Unfortunately, progression to the accelerated phase and/or blastic phase is associated with drug resistance and other poor prognostic features.[8,9] In the blastic phase, CR (or second chronic phase) may be achieved with regimens active in acute lymphoblastic leukemia (ALL) or AML; however, responses are typically short-lived, with an expected survival less than 1 year

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from the onset of blastic crisis.[10] In addition, Ph-negative CML and other myeloproliferative disorders (including idiopathic myelofibrosis [MF] with myeloid metaplasia) are associated with poor prognoses and limited therapy options.[11,12] MF is a poor prognostic factor for patients with CML receiving standard chemotherapy.

Allogeneic BMT offers the best chance for cure of AML, high-risk MDS, CML, and other myeloproliferative disorders. Unfortunately, most patients with these malignancies are not candidates for BMT because of advanced age or other patient-specific characteristics (such as poor performance status).[7] Evaluation of new drugs with novel mechanisms of antineoplastic action is ongoing in an effort to improve outcomes in hematologic disorders associated with a poor prognosis or no standard of care. Interest in agents that inhibit angiogenesis in the bone marrow stroma has recently intensified.

Antiangiogenesis in Hematologic Disorders

Rationale

The rationale for studying antiangiogenesis in hematologic disorders is based on the initial concept that neovascularization (or angiogenesis) is required for the growth of solid tumors.[13,14] The role of angiogenesis has since been established for such malignancies. Until recently, it was uncertain if the growth and proliferation of circulating leukemic cells were angiogenesis dependent.[15] Perez-Atayde et al recently reported that children with ALL have increased bone marrow stroma vascularity and high urinary levels of basic fibroblast growth factor (bFGF; a marker of neovascularization) at diagnosis compared with a control group (children with solid tumors or lymphomas without marrow involvement).[15] The median pretreatment microvessel density (MVD) and the MVD of "hot spots" (single field with highest MVD) were significantly higher ($P < .0001$) in ALL marrows compared with controls. Furthermore, a computer-aided three-dimensional reconstruction model of marrow vascularity showed complex branching of microvessels in ALL marrows; such complex branching was not observed in the control group. Urinary bFGF levels were high in ALL patients before induction chemotherapy, variable during induction, and slightly lower when CR was achieved.

Several studies have shown that angiogenesis accompanies plasma cell growth of monoclonal gammopathies, the progression of B-cell non-Hodgkin's lymphomas, and the activation of multiple myeloma (MM).[16-20] Recently, evaluation of MVD in 36 patients with newly diagnosed MM identified a correlation between MVD and degree of marrow plasmacytosis and cytogenetic abnormalities.[21] Patients with lower mean MVDs experienced longer durations of event-free and overall survival following total therapy (remission induction followed by tandem autotransplants and interferon maintenance) compared with patients with a mean MVD of at least six vessels per field. Overall, these findings suggest that leukemia and other hematologic disorders are angiogenesis-dependent and may be effectively treated with agents that inhibit angiogenesis in the microenvironment.

Antitumor Effects of Thalidomide

During the late 1950s and early 1960s, thalidomide was used as a sedative-hypnotic (increases rapid eye movement [REM] and stage 3-4 sleep[22]) and an antiemetic during pregnancy, until its teratogenic effects were recognized. An increased incidence of limb malformations suggested inhibition of neovascularization in the developing fetal limb bud. Subsequently, D'Amato et al demonstrated direct inhibition of bFGF-stimulated angiogenesis in a rabbit cornea micropocket assay following oral administration of thalidomide.[23] This characterization of thalidomide's mechanism of teratogenicity suggested that the drug may have therapeutic potential in pathologic angiogenesis.

Thalidomide also inhibits tumor necrosis factor-α (TNF-α) production by stimulated monocytes.[24] Clinical efficacy in a wide variety of inflammatory conditions and graft-versus-host disease (GVHD) after allogeneic BMT and renal transplantation suggests that thalidomide possesses immunosuppressive properties.[25-29] Interestingly, a reduced risk of leukemia relapse

has been observed in patients who respond to thalidomide for GVHD.[27] Thalidomide metabolites have demonstrated cytotoxic effects on leukemic cells through induction of morphologic differentiation in vitro.[30]

The similarities between chemotherapeutic agents and thalidomide in terms of teratogenicity prompted clinical investigation of thalidomide's potential as an antineoplastic agent. An early study of thalidomide in various advanced malignancies showed a lack of objective responses[31]; however, preliminary data of more recent studies of thalidomide in the treatment of cancer are encouraging. For example, in a phase I trial of thalidomide for AIDS-related Kaposi's sarcoma (n = 12), two patients achieved partial responses (PRs) and seven had stable disease (SD).[32] In another phase I study, thalidomide (100 mg) was administered to 48 patients with advanced ovarian, renal, breast, or skin cancer; 10 patients had SD (median duration, 12 weeks; range, 8 to 25 weeks).[33] Furthermore, an association was noted between SD and stable/falling serum and urinary vascular endothelial growth factor (VEGF), whereas disease progression was associated with rising VEGF levels.[33] Lastly, thalidomide has demonstrated significant activity as single-agent therapy for high-risk refractory MM and as a component of combination chemotherapy for plasma cell leukemia and fulminant MM.[34,35]

Thalidomide in AML, MDS, and Myeloproliferative Disorders

Pilot studies are being conducted at M.D. Anderson Cancer Center to assess the efficacy and tolerability of thalidomide in refractory/relapsed AML, high-risk MDS, CML, and other myeloproliferative disorders. Additional outcome measures include the effects of thalidomide on bone marrow MVD and serum levels of VEGF and bFGF (data not shown).

Eligibility

Refractory or relapsed AML patients were eligible if the duration of their first CR was less than 12 months. High-risk MDS patients (those with RAEB or RAEB-T) were eligible after failure of frontline therapy (usually combination chemotherapy such as topotecan/cytarabine[4]). CML patients in any phase of disease were eligible; however, patients with chronic-phase were required to have failed interferon-based therapy and be ineligible or unwilling to undergo allogeneic BMT. Those patients with Ph-negative CML and other myeloproliferative disorders (with or without myelofibrosis) were eligible regardless of disease status or previous therapy.

All patients were required to be $\geq$12 years of age and have adequate hepatic and renal function (serum bilirubin and creatinine $\leq$2.5 mg/dL) and a Zubrod performance status $\leq$3. Signed informed consent was required, including agreement of female patients to use safe contraceptive methods during the study period and for at least 4 months after their last thalidomide dose. Patients who were pregnant or lactating were excluded. Those who had a history of seizures, neurotoxicity, serious infections not controlled by antibiotics, or active CNS disease were also ineligible. Concurrent treatment with cytotoxic chemotherapy, biologic therapy, or radiation was not permitted, with the exceptions of hydroxyurea, anagrelide, and granulocyte colony-stimulating factor (G-CSF). G-CSF was indicated if the granulocyte count was $\leq 0.5 \times 10^9$/L due to thalidomide or as required for supportive care in the event of a life-threatening infection.

Dosage and Administration

Thalidomide (50-mg gelatin capsules) was administered orally at an initial daily dose of 200 mg at bedtime. The daily dose was escalated by 200 mg each week if toxicity was $\leq$ grade 0 to 1 (according to the National Cancer Institute criteria) to a maximum daily dose of 800 mg. If grade 2 toxicity occurred, the current dose was maintained until toxicity decreased to $\leq$ grade 1. Grade 2 toxicity persisting longer than 2 weeks resulted in a dose reduction by 1 dose level. If grade 3 to 4 toxicity was observed, thalidomide was held until it was less than grade 3 and was resumed at a lower dose level.

Evaluations

The baseline assessment (performed within 2 weeks of treatment initiation) included a com-

prehensive history and physical examination, hematologic profile, sequential multiple analysis-12 (SMA-12), bone marrow aspirate and biopsy (to assess MVD) with cytogenetics, urinalysis, electrocardiogram, and chest x-ray. Each patient was required to have a hematologic profile, SMA-12, history, and physical examination (including neurologic) every week until reaching a stable maximum dose; the interval between assessments was then lengthened to every 2 to 4 weeks. VEGF and bFGF levels were obtained at baseline and at specified time intervals (depending on diagnosis) during thalidomide therapy. Bone marrow aspirate and biopsy were to be repeated at the end of therapy to determine response or at any time during therapy if disease progression was suspected.

Response Criteria

Patients who received at least 2 weeks of thalidomide therapy were considered evaluable for response. For patients with high-risk MDS or other acute leukemias (AML, RAEB, RAEB-T, chronic myelomonocytic leukemia in transformation [CMML-T], or CML in blastic phase), CR was defined as $\leq$5% blasts in a normocellular or hypercellular marrow with granulocyte count $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L for at least 4 weeks. Complete resolution of extramedullary disease was required for CR.

PR was defined as a reduction of the marrow leukemia infiltrate (MLI = marrow blast percent times cellularity) to less than 20% with correction of the absolute neutrophil and platelet counts (without G-CSF or transfusion support) as defined for CR. Hematologic improvement was defined as achievement of any one of the criteria required for CR where this feature was abnormal prior to therapy (for example, normalization of marrow blasts to $\leq$5%, increase in the absolute neutrophil count to $\geq 1.5 \times 10^9$/L, increase in the platelet count to $\geq 100 \times 10^9$/L) in the AML, MDS, and CML in blastic phase categories. Hematologic improvement in the MPD/MF categories also included the following: (1) $\geq$50% reduction in hepatomegaly and/or splenomegaly, (2) $\geq$50% reduction in packed red blood cell transfusion requirements, and/or (3) $\geq$50% improvement in the neutrophil and/or platelet count. Response outcome was defined as resistant disease if the patient survived the treatment but disease persisted and/or the patient failed to achieve count recovery or other hematologic improvement (such as reduction in transfusion requirements or splenomegaly) within a reasonable time period. Progressive disease (PD) was defined as increasing MLI or peripheral blasts, increasing transfusion requirements, progressive organomegaly, or other such features pertinent to the underlying diagnosis. All patients who had received at least one dose of thalidomide were considered evaluable for toxicity according to the National Cancer Institute criteria.

Results

Demographics

Twenty-eight patients were enrolled from September 1998 to February 1999 (Table 1). The median age of the patient population was 65 years (range, 24 to 85 years); 57% were male, and 25% had performance status $\geq$2.

Overall

Of the 28 enrolled patients, 22 were evaluable for response in that they had received at least 2

Table 1. Specific Diagnoses of 28 Patients Treated With Thalidomide

Diagnosis	No. of Patients
Refractory or relapsing AML	10
Myelodysplastic syndromes	9
RAEB	6
RAEB-T	2
CMML-T	1
Ph-positive CML	4
Late chronic phase	2
Accelerated phase	1
Myeloid blastic phase	1
Other myeloproliferative disorders	5
Ph-negative CML	3
Myeloproliferative disorder with myelofibrosis	1
Idiopathic myelofibrosis	1
Total	28

Abbreviations: AML, acute myeloid leukemia; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation; CMML-T, chronic myelomonocytic leukemia in transformation; CML, chronic myeloid leukemia; Ph, Philadelphia chromosome.

Table 2. Adverse Effects Reported During Treatment With Thalidomide

Adverse Effect	No. (%) of Patients
Fatigue	16 (57)
Neurotoxicity, reversible	12 (43)
Sedation, grade 1 or 2	7
Confusion, grade 2	2
Paresthesias, grade 2	2
Orthostasis, grade 2	1
Gastrointestinal toxicity	12 (43)
Emesis, grade 1 or 2	2
Constipation, grade 1 or 2	10
Rash or skin dryness	9 (32)
Infection	7 (25)
Pneumonia	3
Cytomegalovirus	1
Cellulitis	1
Gastroenteritis	1
Chronic foot ulcer	1

weeks of therapy. Six patients continued thalidomide, with a median treatment duration of 3 months (range, 1 to 5 months). Sixty-four percent of patients achieved a dose of at least 600 mg daily. Reasons for discontinuing thalidomide among evaluable patients included failure to respond after 1 month of therapy (n = 7), development of PD (n = 3), toxicity (n = 2; fatigue/crying spells, confusion), and death (n = 4). Of the six patients who were inevaluable, three had rapidly PD and three requested discontinuation of therapy for one of the following reasons: (1) inability to swallow the medication, (2) emesis, and (3) severe fatigue.

The adverse effects reported during treatment with thalidomide are summarized in Table 2. Adverse effects generally were mild to moderate (grade 1 or 2). Overall, fatigue was the most common adverse effect and was dose-limiting. Twenty-one percent of patients required a dose reduction due to fatigue or sedation. Constipation was manageable with the use of laxatives. Most infections observed occurred in thalidomide nonresponders with AML or MDS who had prolonged neutropenia. A chronic foot ulcer in one patient was felt to be related to concomitant hydroxyurea.

Four patients (with AML or high-risk MDS) died during the study. Probable causes of death included arrhythmia (n = 1), pneumonia resulting in respiratory arrest (n = 1), and pulmonary hemorrhage resulting in sudden death (n = 1). The relationships between thalidomide therapy and these fatalities were not established. In one patient, circumstances surrounding the death were unknown.

AML

Of the 10 patients with AML enrolled, eight (80%) achieved prior CR with standard first-line chemotherapy (median duration, 10 months; range, 5 to 24 months). The median number of prior salvage regimens received was 1 (range, 0 to 5). Four patients received thalidomide as their first salvage attempt.

The median duration of treatment on study was 1 month (range, 12 days to 3 months). Thalidomide daily doses of 800 mg and 600 mg were reached by four and two patients, respectively. Of the nine evaluable AML patients, one patient achieved hematologic improvement, three had no response (one with transient reduction in MLI), three had PD, and two died. The following case summarizes the experience of the patient with AML who experienced hematologic improvement:

A 51-year-old woman with diploid karyotype AML (diagnosed in June 1997) initially achieved CR with induction chemotherapy (ifosfamide, cisplatin, and etoposide) followed by consolidation and autologous BMT. She relapsed in February 1998 after a CR duration of approximately 7 months. Combination chemotherapy with fludarabine, cytarabine, and G-CSF produced a second CR of short duration. Subsequently, she received two salvage regimens (idarubicin/hydroxyurea, then cyclophosphamide/cytarabine/topotecan/G-CSF) that did not produce adequate responses.

In December 1998, she had proliferative disease requiring leukapheresis and hydroxyurea. She was started on thalidomide 200 mg daily, at which time her white blood cell (WBC) count was 18 $\times$ 10^9/L with 85% blasts. Bone marrow biopsy revealed 73% blasts, 80% cellularity, and an MLI of 58. After 2 weeks of therapy, she developed a left peripheral seventh nerve palsy and was confirmed to have CNS disease. Intrathecal cytarabine, dexamethasone, and radiation therapy were administered. Thalidomide was continued at 200 mg daily; it could not be escalated because of persistent fatigue and occasional emesis requiring pre-dose antiemetics. Hydroxyurea was discontinued with a decreasing WBC count.

Day 29 bone marrow biopsy showed reduced blasts (11%), cellularity (50%), and MLI (5.5).

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